TARGETED

GENETICS

November 21, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

RE: [Docket Number 2005D-0310] *Draft Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events*

Targeted Genetics Corporation (TGC) develops gene-based therapies to prevent or treat acquired, inherited and infectious diseases. We applaud the FDA's efforts in developing this draft guidance document and appreciate the opportunity to provide comments. We believe that this document will assist both industry and the agency in setting reasonable science-based expectations for long-term follow-up requirements in this rapidly evolving field.

General Comments

TGC strongly supports the development of this guidance document. We actively participated in the June 2004 workshop in conjunction with the ASGT annual meeting and are encouraged that the agency was receptive to many of the points raised in the course of the workshop. However, the draft guidance is silent regarding several of the issues raised at the workshop.

1) No guidance is provided regarding at which phase of clinical development long-term follow-up should be implemented. Our position remains that, should long-term follow-up be recommended on a case-by-case basis for a specific vector other than those vectors with a high risk of insertional mutagenesis, the most effective point to obtain meaningful data would be at post-marketing surveillance.

2) There is no specific guidance regarding the criteria or methodology for detecting and determining whether a delayed adverse event is gene therapy-related. The term gene therapy-related is not defined. Please provide examples of observed delayed adverse events considered to be gene therapy-related, other than those associated with insertional mutagenesis.

3) We question the scientific value of the recommended physical examinations for the first five years of long-term follow-up. At the workshop Dr. Rosenblum from FDA/CBER articulated that the purpose of these exams was to document established

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disorders, not to search for evidence of undiagnosed syndromes. Annual telephone contact would be sufficient to document established disorders. The guidance in the draft document as written may be interpreted as a requirement to rule out a laundry list of potential oncologic, neurologic, autoimmune and hematologic disorders at each scheduled visit.

4) We strongly agree that not all subject populations are suitable for collection of scientifically meaningful long-term follow-up data due to short life expectancy, co-morbidities or exposure to other agents.

Specific Comments

Section III.DEFINITIONS AND ABBREVIATIONS
Transgene: An exogenous gene that is introduced into a host genome.

Comment: Given that many genes used in the context of gene therapy trials are not intended to integrate into the host genome we recommend that this definition be revised to read "*An exogenous gene that is introduced into a host cell*".

Section IV.A. Paragraph 2): "Similarly, if sufficient data accumulate to suggest that your product is not associated with delayed risks, it may be appropriate to reduce or eliminate provisions for long-term follow-up observations."

Comment: Please clarify if this guidance may be applied to clinical studies which have already completed the active phase and are considered closed except for long-term follow-up commitments. If so, please provide guidance as to whether an IND amendment to indicate changes to long-term follow-up plans would be sufficient, or if an amendment to each individual clinical protocol would be expected.

Section IV.B.4 Considerations for Preclinical Study Design to Assess Vector Persistence

"...If possible and applicable, we recommend that the studies employ an animal species that permits vector transduction and/or vector replication and that the animal species be biologically responsive to the specific transgene of interest..."

Comment: Please provide guidance for alternatives if a suitable animal species is not available for long-term studies. For example, if the animal species is biologically responsive to the vector product but also mounts an immune response which would not be expected in a human population, would use of a species-specific transgene be recommended?

Section V.B Suitability of Clinical Trial Populations for Long-term Follow-up Observations

Comment: We strongly agree that some populations would not provide scientifically useful long-term follow-up data due to the confounding factors of exposure to other agents, short life expectancies or co-morbidities.

Minor Typographical Errors

Section IV.C Table 1, Footnote 2
"...to mitigate risis to subjects..." should be corrected to read "...to mitigate risks to subjects..."

The document is inconsistent in the use of hyphenation for "long-term follow-up".

We welcome the opportunity to provide feedback on the *Draft Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events* and look forward to implementation of these guidelines. Please contact me if you require clarification or further information regarding our comments.

Sincerely,

Rae Saltzstein
Director, Quality and Regulatory Affairs
Targeted Genetics Corporation